SECTION THREE

Description of the new dietary ingredient creatine from creatine ethyl ester hydrochloride (HCl). See 21 CFR Section 190.6 (b)(3).

See the enclosed Attachments 1, 2, and 3, product specifications, certificate of analysis, and test methods developed by the University of Nebraska Medical Center, College of Pharmacy, which include:

1. Attachment 1: Product Standard Specification Sheet for the purity of the creatine source creatine ethyl ester HCl; a Certificate of Analysis from and a description of the testing methods developed by the University of Nebraska Medical Center, and two historical references cited on the preparation of creatine ethyl ester HCl, Lacamas Laboratories and Biovance Technologies Standard Specification and Biovance Technologies (CEE-HCL) HPLC Method.
2. Attachment 2: Material Safety Data Sheet for the creatine source creatine ethyl ester HCl prepared by Lacamas Laboratories.
3. Attachment 3: Heavy metal and organic solvent analyses from Midwest Laboratories performed on an experimental lot of the creatine source creatine ethyl ester HCl to assist in the validation of the synthetic process to be used for the commercial manufacture.

Company relationships

Biovance Technologies, Inc. (11515 North 84th Street, Omaha, NE 68122) a privately-held biotechnology company, has contracted with ChemPharma International (300 Provider Court, Suite 200, Richmond, KY 40475), a contract research organization, to provide, under license, creatine source creatine ethyl ester HCl for Biovance. ChemPharma, has in turn, executed a commercial supply contract with Lacamas Laboratories. Biovance has entered into a distribution contract with Medical Research Institute, who will be responsible for the final manufacturing and distribution. Lacamas will produce the creatine source creatine ethyl ester HCl using quality control specifications provided to them by Biovance. Biovance has in turn used the identical quality control specifications for the Biovance-Medical Research Institute distribution agreement.

Manufacturing process and quality assurance testing

Creatine from creatine ethyl ester HCl will be manufactured in separate batches (lots) under cGMP conditions by Lacamas Laboratories (Portland,

OR), and will be supplied exclusively to Medical Research Institute enclosed and contained in vacuum-sealed, plastic-lined PVC 20-kilo drums for use as a bulk raw material.

Lacamas will take an appropriate sample quantity from each and every batch for quality control/quality assurance testing. The sample for quality testing will be subdivided for testing by Lacamas and by the University of Nebraska Medical Center (performed under contract with Biovance). Every batch of the final bulk creatine source product will consist of at least 96% creatine ethyl ester HCl, with creatine and creatinine constituting the remaining material. The content of creatine source creatine ethyl ester HCl in each lot will be determined independently by Lacamas and the University of Nebraska Medical Center using a validated high performance liquid chromatography (HPLC) assay. The University of Nebraska Medical Center has also developed additional assays (Nuclear Magnetic Resonance) for product purity, which will be used to confirm the results of their HPLC analysis.

Upon the completion of the quality control assays with an acceptable result from each testing location (passing the product specification for purity; see above), the bulk product will be released by Lacamas to Biovance, who in turn will release the bulk creatine source material creatine ethyl ester HCl to Medical Research Institute for final manufacturing under the terms and conditions of the Biovance-Medical Research Institute distribution agreement.

Creatine from creatine ethyl ester HCl will be distributed by Medical Research Institute in capsules, caplets, or tablets containing 500, 750, or 1000 mg creatine, and as a bulk raw material powder (in vacuum-sealed, plastic-lined PVC 20-kilo drums) for use as a dietary ingredient in dietary supplement products.